

# **ACIP Anthrax Vaccine Work Group**

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# **REVIEW “ANIMAL RULE” AND CORRELATES OF PROTECTION MODEL**

## Predicting Human Survival Based on “Animal Rule” Data

- ❑ Data from animal challenge studies was used to generate a correlate of protection model to predict survival based on the measured immune response to vaccination
- ❑ The model was applied to human clinical trial data to predict the level of protection in the human cohorts
- ❑ The predicted survival levels generated are indirect measures, therefore the data was downgraded to reflect the lack of direct measurement of protection in humans

## **Data Used to Determine AVA Effectiveness Based on “Animal Rule” Data**

- ❑ Animal survival data (Sivko, 2016)
  - Supporting data (Quinn, 2012; Ionin, 2013)
- ❑ Immune response in humans
  - Subset of a pre-exposure (0, 14 and 28 days, then 6, 12, and 18 months) regimen study used to compare IM vs SC route of administration (Wright, 2014)
  - Dose sparing schedules (Bernstein, 2014)
    - 2 full doses at 0 and 14 days
    - 2 full doses at 0 and 28 days
    - 3 half doses at 0, 14, and 28 days

# **QUESTIONS FOR ACIP COMMITTEE**

# Summary of Policy Questions for ACIP Consideration

## Optimizing use of vaccine during a large mass vaccination event

- 1) May the intramuscular (IM) route of administration (ROA) be used if the subcutaneous (SC) ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?
- 2) Should there be an inadequate supply of anthrax vaccine available for PEP, may either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?

## Use of antimicrobials in conjunction with vaccine

- 3) In immunocompetent individuals who are being vaccinated with anthrax vaccine, do antimicrobials provide adequate protection when given for:
  - a) At least 42 days after the first vaccine dose, or
  - b) 2 weeks after the last vaccine dose, whichever comes later

**GRADE**

# Nonhuman Primate Studies

Author, year	Study design (# enrolled)	Interventions
Sivko, 2016	RCT (48)	<ul style="list-style-type: none"> <li>• Vaccinated with serial dilutions of AVA on Days 0 and 14</li> <li>• Challenged with 205 LD<sub>50</sub> <i>Bacillus anthracis</i> spores on Day 28</li> <li>• Survival</li> </ul>
Ionin, 2013	RCT (48)	<ul style="list-style-type: none"> <li>• Vaccinated with serial dilutions of AVA on Days 0 and 28</li> <li>• Challenged with 200 LD<sub>50</sub> <i>Bacillus anthracis</i> spores on Day 70</li> <li>• Survival</li> </ul>
Quinn, 2012	RCT (114)	<ul style="list-style-type: none"> <li>• Vaccinated with serial dilutions of AVA on Days 0 and 14</li> <li>• Challenged with 200-400 LD<sub>50</sub> <i>Bacillus anthracis</i> spores at 12, 30, or 52 months</li> <li>• Survival</li> </ul>

# Human Immunogenicity / AE Studies

Author, year	Study design (# enrolled)	Interventions/Outcomes
Immunogenicity and AE Studies		
Wright, 2014 (direct comparison IM vs SC ROA)	RCT (781)	AVA given: <ul style="list-style-type: none"> <li>• Subcutaneous (SC) at days 0, 14, and 28</li> <li>• Intramuscular (IM) at days 0, 14, and 28</li> </ul> Anti-PA IgG concentration at days 0, 28, and 56
Bernstein, 2014 (Dose-sparing schedules)	RCT (328)	AVA given: <ul style="list-style-type: none"> <li>• Full dose at days 0, 14</li> <li>• Full dose at days 0, 28</li> <li>• Half-dose at days 0, 14, and 28</li> <li>• Full dose at days 0, 14, and 28</li> </ul> Anti-PA IgG concentration at days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70

# Human Immunogenicity / AE Studies cont'd

Author, year	Study design (# enrolled)	Interventions/Outcomes
<b>Immunogenicity and AE Studies</b>		
Hopkins, 2014	Obs (200)	<ul style="list-style-type: none"> <li>AVA full dose at days 0, 14, and 28</li> <li>Anti-PA IgG concentration at days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70</li> </ul>
Rynkiewicz, 2011	RCT (69)	<ul style="list-style-type: none"> <li>AVA full dose at days 0, 14, and 28</li> <li>Anti-PA IgG concentration at days 0, 7, 14, 21, 28, 35, 42, 49, and 56</li> </ul>
King, 2015	Obs (321)	<ul style="list-style-type: none"> <li>AVA full dose at days 0, 14, and 28</li> <li>Anti-PA IgG concentration at days 28 and 56</li> </ul>
Zhang, 2008	Obs (128)	<ul style="list-style-type: none"> <li>Six AVA full doses on pre-exposure schedule</li> <li>Anti-PA IgG concentration immediately prior to AVA dose</li> </ul>
<b>Immunogenicity Studies only</b>		
Ionin, 2013	Obs (150)	<ul style="list-style-type: none"> <li>AVA full dose at days 0, 14, and 28</li> <li>Anti-PA IgG concentration at days 0, 7, 14, 21, 28, 35, 42, 49, 56, 63, and 70</li> </ul>
Minang, 2014	RCT (200)	<ul style="list-style-type: none"> <li>AVA full dose at days 0, 14, and 28</li> <li>Anti-PA IgG concentration at days 0, 14, 28, 42, and 70</li> </ul>

# Policy Question for ACIP to Consider

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## **Policy Question 1: May the intramuscular (IM) route of administration (ROA) be used if the subcutaneous (SC) ROA presents clinical, operational, or logistical challenges that may delay or prevent effective vaccination?**

Populations	Healthy Adults (18-65 y/o)
Interventions	3 doses of AVA administered IM at 0, 2, and 4 weeks
Comparison	3 doses of AVA administered SC at 0, 2, and 4 weeks (current licensed schedule)
Outcomes	Immunogenicity Adverse Events

## IM ROA as an alternative to SC ROA

Outcome	Design (# studies	Initial Evidence	Bias Risk	Inconsistent	Indirect	Imprecise	Pub Bias	Others	Final Evidence	Overall Evidence Type
Benefits										
Immune response	RCT (4)	1	No	None	Yes (-1)	None	None	None	2	2
	OBS (4)	3	No	None	Yes (-1)	None	None	SOA +1 DR +1	2	
Harm										
Adverse Events	RCT (3)	1	No	None	None	None	None	None	1	1
	OBS (3)	3	No	None	Yes (-1)	None	None	DR +1	3	

SOA – Strength of Association

DR – Dose Response

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## Policy Question 2: Should there be an inadequate supply of anthrax vaccine available for PEP, can either 2 full doses or 3 half doses of AVA be used to expand vaccine coverage?

Populations	Healthy Adults (18-65 y/o)
Interventions	<ul style="list-style-type: none"><li>• 2 full doses of AVA administered SC at 0 and 2 weeks</li><li>• 2 full doses of AVA administered SC at 0 and 4 weeks</li><li>• 3 half doses of AVA administered SC at 0, 2, and 4 weeks</li></ul>
Comparison	3 doses of AVA administered SC at 0, 2, and 4 weeks (current licensed schedule)
Outcomes	Immunogenicity

# Dose-sparing Strategies

2 Full Doses at 0 and 2 weeks  
 2 Full Doses at 0 and 4 weeks  
 3 Half Doses at 0, 2, and 4 weeks

Outcome	Design (# studies)	Initial Evidence	Bias Risk	Inconsistent	Indirect	Imprecise	Pub Bias	Others	Final Evidence	Overall Evidence
Immune response	<u>Human Data</u>									2
	RTC (1)	1	No	None	Yes (-1)	None	None	None	2	
	<u>Non-human Primate Data</u>									
	RCT (3)	1	No	None	Yes (-2)	None	None	None	3	

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## Policy Question 3: Can the antimicrobial component of PEP be decreased to less than 60 days?

Populations	Healthy Adults
Intervention	<ul style="list-style-type: none"><li>• 2 full doses of AVA administered SC at 0 and 2 weeks</li><li>• 2 full doses of AVA administered SC at 0 and 4 weeks</li><li>• 3 half doses of AVA administered SC at 0, 2, and 4 weeks</li><li>• 3 doses of AVA administered SC at 0, 2, and 4 weeks (current licensed schedule)</li></ul>
Comparison	Placebo or no vaccination
Outcomes	Immunogenicity

# Antimicrobial Duration for PEP

2 Full Doses at 0 and 2 weeks  
 2 Full Doses at 0 and 4 weeks  
 3 Half Doses at 0, 2, and 4 weeks

Outcome	Design (# studies)	Initial Evidence	Bias Risk	Inconsistent	Indirect	Imprecise	Pub Bias	Others	Final Evidence	Overall Evidence
Immune response	<u>Human Data</u>									2
	RTC (1)	1	No	None	Yes (-1)	None	None	None	2	
	<u>Non-human Primate Data</u>									
	RCT (3)	1	No	None	Yes (-2)	None	None	None	3	

# Antimicrobial Duration for PEP

## 3 Full Doses at 0, 2 and 4 weeks

Outcome	Design (# studies)	Initial Evidence	Bias Risk	Inconsistent	Indirect	Imprecision	Publication Bias	Others	Final Evidence	Overall Evidence Type
Immune response	<u>Human Data</u>									2
	RCT (4)	1	No	None	Yes (-1)	None	None	None	2	
	OBS (4)	3	No	None	Yes (-1)	None	None	None	2	
	Non-human Primate Data									
	RCT (3)	1	No	None	Yes (-2)	None	None	None	3	

SOA – Strength of Association

DR – Dose Response

## GRADE Summary

Policy Change	Overall GRADE	
IM ROA as an alternative to SC ROA	Benefit	2
	Harm	1
Dose-sparing strategies	Benefit	2
	Harm	N/A
Antimicrobial duration for PEP	Benefit	2
	Harm	N/A